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RE: **Summary of Key Concerns Regarding the Epidemiological Studies Reported in the IRIS Draft Formaldehyde Document**

Dear Members of the NAS Committee:

The undersigned prepared comments which were presented to your Committee by some of on August 9, 2010, during the allocated public comment period. Collectively, we expressed several concerns regarding the IRIS draft document, specifically pertaining to formaldehyde as a leukemogen. We understand and appreciate that the Committee has been evaluating the draft IRIS document, and has considered the points we raised. However, because the five minutes we each were given was too short to articulate all key epidemiological points, we are providing this brief summary for your consideration.

IRIS review methodological issues

1. The standard criteria used to critically review individual epidemiological studies are not transparent.
2. Inconsistencies in results identified across studies appear not to be addressed in the synthesis of evidence, and therefore not reflected in the conclusions.
3. The methodology for synthesizing epidemiological evidence across relevant studies is not clear.
4. Although strengths and weaknesses of the various articles are discussed, the criteria for determining relative study weights are not transparent.
5. Overlapping cohorts and studies are not properly identified and discounted.
6. Some papers have been overlooked or excluded without justification.
7. There is a lack of consistency across exposure metrics (including contradictory evidence such as 'ever peak' vs. 'cumulative peak' exposures) within and across studies.
8. The consequences of combining evidence across studies with non-comparable exposures and inconsistent exposure metrics have not been addressed.
9. Summary tables depicting evidence on which conclusions are based are lacking.
10. Causal conclusions are offered for combinations of unrelated diseases of differing etiologies – e.g., all lymphohematopoietic cancers combined, all leukemias combined and all myeloid leukemias combined.
11. Undue weight is placed on selected studies of embalmers (i.e., three PMR studies and case-control study based on these cases), plus the Zhang meta-analysis.
12. Preferential identification of "positive" associations or "increased" risks (many not statistically significant) is relied upon in formulating causal conclusions.

13. Perhaps most crucial is that EPA's causal conclusions do not clearly follow from their own critical review of the individual studies.
14. Ultimately, the IRIS draft does not appreciate that the body of study findings is predominantly negative when a proper "weighting" of the evidence is considered. It is especially striking that the strong evidence of no increased risk based on the three largest cohort studies combined (152 observed and 153 expected leukemia cases) is afforded little weight and that the considerably weaker Hauptmann 2009 report is repeatedly highlighted.

Critical points pertaining to influential studies in IRIS Draft

Beane Freeman 2009

1. Supplemental material is published on-line that corrects the results from Hauptman 2003, including 995 (erroneously reported as 1006) previously omitted deaths. This should be highlighted.
2. No excesses of leukemia or myeloid leukemia deaths are reported in this study.
3. Quantitative exposure estimates based on industrial hygiene measurements generate no consistent exposure-response relationships. Whereas "ever peak" exposure produces a positive association, no association is seen (and results not shown) for "cumulative peak" exposure, a more accurate indicator of high exposure.
4. The percentage of statistically significant tests reported (3/36 or 8.3%) is close to what would be expected (5%) by chance alone.

Zhang 2009

5. This meta-analysis does not follow standard methods for selection of data from studies.
6. Data are combined across studies for the "highest exposed" category from each, regardless of the comparability of exposure metric.
7. Studies with overlapping (non-independent) populations have been included.
8. The meta-analysis does not include the Beane Freeman 2009 study.

Hauptmann 2009

9. This study relies on convenience sample of death certificates from several previous reports.
10. Cases were identified based on both contributing and underlying causes of death.
11. Many death certificates reflected coding practices and diagnostic criteria from previous decades and may not be comparable over time.
12. The study data do not demonstrate an excess of myeloid leukemia: PMR=108, 95% CI 72-156 (Cole 2010, in press).
13. Surrogate exposure information was obtained from next-of-kin or co-workers, often pertaining to decedents' work practices from several decades earlier and subject to recall bias.
14. Myeloid leukemia cases differed from controls in several ways, possibly reflecting selection forces: cases were first employed earlier (52% more likely employed prior to 1942) longer, and at a younger age; cases had earlier typical year of death (subject to diagnostic and coding conventions of the 1960's and 1970's); cases had higher number of embalming and estimated cumulative exposure (possibly reflecting differences in employment duration); and all cases were of white race.

15. On the other hand, myeloid leukemia cases were similar to controls with respect to the following key exposure indicators: average formaldehyde estimates; TWA 8-hour exposure estimates; and peak formaldehyde exposure estimates.
16. For myeloid leukemias, the reference group suffered from extremely small numbers, leading to two sets of analyses. Initial findings using the unexposed as referent – which only contains one myeloid death – yields highly unstable risk estimates; therefore the referent group is re-set to include those having conducted 500 or fewer embalming. Basis for selecting 500 as "unexposed" is not evident.
17. The second set of analyses, using the expanded reference group and generating more stable estimates, does not demonstrate dose-response relationships across exposure categories for most exposure surrogates.
18. Tests for trend, based on an analysis that is not presented, are juxtaposed with results from both the first and second analyses, which is misleading, as they appear to apply to the presented results.
19. Interpretation of the study OR's is difficult, since the study base does not represent a specified cohort's person-time, cases represent only those identified from available death certificates, and controls could not be randomly sampled from the actual cohort that generated cases.
20. Other case-control studies on this subject were based on registry cases (e.g., Blair 2001, Partanen 2003), with more comprehensive and verifiable diagnostic data. These studies found little evidence of an association between formaldehyde exposure and leukemias or myeloid leukemias.

<u>Omissions from IRIS Draft relevant to leukemia discussion</u>

Bachand 2010

1. This is the only meta-analysis on this topic that used standard methods and included Beane Freeman 2009.
2. More sensitivity analyses are presented than in any other meta-analysis, and the associations between formaldehyde and leukemia and myeloid leukemia are not robust.

Marsh 2004

3. This re-analysis of the data from Hauptmann 2003 demonstrates unusually low disease rates in the reference group used in internal exposure-response analyses.
4. The results bring into question the suggestion made in Hauptmann 2003 that the observed associations reflect a causal relationship.

Marsh 2010

5. This re-analysis demonstrates the impact of NCI's omission of 995 deaths (12% of all deaths) on the study results.
6. The corrected analyses show attenuated associations because the omitted observed deaths disproportionately occurred among unexposed employees.
7. The re-analysis also demonstrates latent periods that are implausibly longer than those observed related to other chemical exposures such as chemotherapeutic agents.

Lu 2010

15. The Lu 2010 study, though not an epidemiological study, helps explain the general lack of observed excesses of leukemia, especially given that formaldehyde appears to be incapable of reaching blood-forming tissues.

We appreciate your interest and consideration. Please do not hesitate to contact any of us should you have any questions or if any of these points is unclear.

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